Collaborating to Move Research Forward

The Bladder Cancer Advocacy Network hosted the 10th Bladder Cancer Think Tank from August 6 – 8, 2015 in Charlotte, NC. This meeting is an essential vehicle for advancing collaborative research efforts in bladder cancer. The meeting was Chaired by Dr. Ashish M. Kamat from MD Anderson Cancer Center, Houston and Dr. Jonathan Rosenberg from Memorial Sloan Kettering Cancer Center, New York. The meeting attracted over 200 attendees representing nearly 80 prestigious medical institutions and five countries.

Think Tank expert panels, group discussions, and networking opportunities help to generate ideas and strengthen collaborations between researchers and physicians across disciplines and between institutions. Interactive panel discussions addressed a variety of timely issues: data sharing, privacy and social media; improving patient navigation through therapy; promising developments in immunotherapy; and moving bladder cancer research from bench to bedside. Importantly, early career researchers presented their bladder cancer studies and had opportunities to network with leading experts.

Dr. James Doroshow, Director of Division of Cancer Treatment and Diagnosis, Deputy Director for Clinical and Translational Research at the National Cancer Institute, delivered the keynote address on reducing the timeline for developing cancer drugs. Stressing that most clinical trials fail because the tested drug does not work, Doroshow highlighted the role of molecular pharmacodynamics in shortening this timeline and advised researchers that new oncology drugs must demonstrate relevant downstream pharmacologic effect (cell kill) at the site of action. This proof of mechanism (POM) must be assessed to move drug development forward. Doroshow also addressed some of the difficulties in research related to combination therapies and the development of multiplex pharmacodynamics assays that can measure entire pathways with a single biopsy.

The future of bladder cancer diagnostics and treatment is brighter than it has been in decades. The number of new clinical trials underway in all areas of bladder cancer research is increasing. The Think Tank continues to create an environment that allows research ideas to develop and expand. The culture of collaboration displayed at the Think Tank is helping to accelerate progress in improving the diagnosis, treatment, and quality of life for people impacted by bladder cancer.

Thank you to our generous 2015 Think Tank partners: Abbott Molecular, Inc.; Bristol-Myers Squibb; Genentech: A Member of the Roche Group; Heat Biologics; IOS Press; KARL STORZ Endoscopy-America; Merck; Olympus; OncoGenex; Pacific Edge Diagnostics LTD; Photocure; Taris Biomedical; TheraCoat; Telesta Therapeutics; and Viventia Bio, Inc.
The increased use and popularity of social media provides new opportunities for patient engagement in their medical care and treatment. The availability of “big data” - massive data sets that include predictive analyses and practice patterns - may hold the key to more efficient and higher-quality health care delivery. The promise of these new tools, however, also presents significant ethical and policy questions involving patient privacy and security. Moreover, understanding how to use big data and bioinformatics effectively is essential to ensure that scientific results are conveyed accurately.

Dr. David Cooke of the University of California Davis presented examples from his web-based social media lung cancer patient engagement tools. Noting that most social media platforms are now mobile-based to reach a wider audience, Cooke advised participants to follow the “POST” methodology before launching a social media community. POST refers to People - know your audience; Objectives - define goals and endpoints; Strategy - plan how you want to interact online; Technologies - pick a platform that works with your strategy. Explaining that social media such as Twitter is an “instant press conference,” Cooke urged attendees to consider the Health Insurance Portability and Accountability Act (HIPAA) regulations as they venture into social media for patient engagement. Dr. Cooke also discussed the benefits to using social media to inform patients about research articles and clinical trials, noting that this may encourage medical journals to provide open-sourced access to the peer-reviewed articles.

Dr. David Miller discussed the Michigan Urological Surgery Improvement Collaborative (MUSIC), a physician-led quality improvement collaborative. MUSIC is a consortium of 42 urology practices across the state of Michigan, covering over 85-90% of Michigan urologists designed to evaluate and improve the quality and cost-efficiency of prostate cancer care for men in Michigan, using “big data” to improve practice patterns. MUSIC provides a scalable approach to primary data collection and identifies the challenges and opportunities to improve the quality of care. Miller addressed HIPAA business associates regulatory requirements, data collection through abstraction and a statewide registry. The MUSIC data includes patient-reported outcomes (PRO) through validated surveys, performance reports to surgeons and real-time reports for clinical data. Miller sees opportunities for similar data sharing in bladder cancer. Miller urged participants to follow the principle of “collecting what you need and needing what you collect.”

M.D. Anderson Cancer Center’s bioinformaticist Keith Baggerly, Ph.D., stressed the importance of simple tests with big data because “our intuition about what ‘makes sense’ is very poor in high dimensions.” Baggerly explained that to use “omic-based signatures” (such as genomics or proteomics) as biomarkers, researchers need to know they have been assembled correctly. Using forensic bioinformatics, Baggerly described in detail how researchers incorrectly interpreted data from specific high profile studies designed to predict which patients would respond to chemotherapeutics based on genomic data. These studies were published in high impact scholarly journals, and clinical trials were established based on the studies. The articles were later retracted, and the trials halted. Baggerly discussed the difficulty in replicating study results, noting the most common mistakes include confounding the experimental design and mixing up sample, gene, or group labels. Baggerly urged researchers to use rigorous processes to analyze the quality of data because the most common mistakes are simple and often hidden due to incomplete documentation.
Session Two: Patient Navigation through Therapy
Panel Co-Chairs: Sia Daneshmand, M.D., University of Southern California; Jay Shah, M.D., MD Anderson Cancer Center

“Patient Perspective” David Langham, Randy Layne, Jacqueline Nalls, Howard R. Merriman

“Delivering Coordinated Patient-Centered Care: The Value of Multidisciplinary Bladder Cancer Clinics for Team-based Care” William Shipley, M.D., Massachusetts General Hospital

“Incorporation of Patient Preference in Decision Making” Donna Berry, Ph.D., RN, Dana-Farber Cancer Center

“The Optimized Surgical Journey” Jay Shah, M.D., MD Anderson Cancer Center

“How Should We Measure Success in Bladder Cancer Patients?” Scott Gilbert, M.D., MS, H. Lee Moffitt Cancer Center and Research Institute

“Point-counterpoint on Management of HGT1” Sia Daneshmand, M.D., University of Southern California and Ashish Kamat, M.D., MD Anderson Cancer Center

From initial diagnosis through treatment, bladder cancer patients and their families must navigate and manage a complex healthcare system and numerous treatment decisions. The focus of this session was to identify the challenges and discuss ways to improve the patient journey and treatment outcomes. This panel opened with four patients providing their unique perspective on their treatment decision making. They addressed their personal navigation of treatment options, making a diversion choice, the impact of treatment decisions on sexual functioning, and bladder preservation.

William Shipley, M.D., noted that from the patient’s perspective “a decision about me, without me” is not right. He highlighted the team-based approach which includes the patient and family voice to accommodate treatment choices and outcomes that are best for achieving what the patient wants. Shipley noted that the multi-disciplinary clinic enhances the consideration of evidence-based medicine and can increase treatment adherence and enhance clinical trial accrual.

Dana-Farber Cancer Center nurse Donna Berry, Ph.D., discussed her research on patient navigation through therapy, focusing on the path to patient-centered decision making in muscle invasive stage I and II bladder cancer. She shared results of a study examining sixty patients’ treatment decision-making process using grounded theory methods of data analysis. Patients with various stages of bladder cancer described a complex treatment decision process that began with them seeking a cancer “Center of Excellence”. Berry noted patients combined physician recommendations with information about treatment success rates and their personal attributes when considering bladder reconstruction options.

Jay Shah, M.D., noting the high complication rates associated with radical cystectomy, explained the need for patient navigation through the decision-making process. He explained how the Enhanced Recovery After Surgery® (ERAS) guidelines for pre-, intra- and post-operative care could reduce complications and get patients out of the hospital in a shorter period. Shah, using a similar set of guidelines (the Optimized Surgical Journey) at MD Anderson, sees post-operative milestones achieved earlier; to improve patient care and reduce healthcare costs. While focusing on hospital-centered outcomes is only “part of the goal” Shah stressed that there is a need to understand better and measure the patient’s symptom burden. He explained that MD Anderson uses a "symptom inventory"-- MDASI--to assess patient-centered outcomes. Using the MDASI, patients who were part of the OSJ program reported improvement in certain significant areas, including abdominal discomfort, impairment of general activity, mood and relationship impairment and overall greater enjoyment of life. However, in other areas, the use of OSJ did not improve the patient experience. Measuring this data presents opportunities to improve patient reported and hospital-centric outcomes. Shah noted that MD Anderson is developing a bladder cancer-specific MDASI, with the goal of better understanding the patient surgical experience, to better navigate through radical cystectomy.

The Moffit Cancer Center’s Scott Gilbert, M.D., MS, presented the metrics used for measuring success among bladder cancer cystectomy patients. Traditional measures of success include the length of survival, response to therapy, complications/adverse events, recurrence or re-admission rates and functional outcomes. Gilbert suggested alternative measures to the quality of care, stressing the role of patient preferences and perspectives on the outcomes. Patient-reported outcomes (PROs) include any report of the status of a patient’s health condition
that comes directly from the patient. Gilbert reminded participants that PROs do not include interpretation of the patient’s response by a clinician or anyone else. He stressed PROs can reflect health states/conditions that warrant additional investigation. PROs can often correlate with quality of life outcomes, particularly after cystectomy. Gilbert suggested ways PROs could be integrated into care settings to help manage symptom distress.

To conclude this panel, Drs. Daneshmand and Kamat debated the management of a common dilemma facing bladder cancer patients - that of high-grade T1 (HGT1) bladder cancer. Kamat noted the American Urological Association (AUA) and the European Association of Urology (EAU) recommend BCG as a primary option for most HGT1 bladder cancer in their respective guidelines. New data suggest that most patients do not progress and have good survival statistics with BCG maintenance compared to older data. He then went on to debunk some reasons why urologists may not recommend BCG for HGT1 bladder cancer and stressed that radical cystectomy is not a benign procedure. Daneshmand provided a different perspective noting that high-grade urothelial carcinoma of the bladder does not have a step-wise progression but is a potentially lethal disease. It requires meticulous attention to achieve optimal patient outcomes. He shared data noting if one waits until muscle invasion is clinically evident, cure rates may drop significantly. Both Kamat and Daneshmand identified decision factors to consider in making the choice between BCG and cystectomy for high-grade T1 bladder cancer. These include associated CIS; deep lamina propria invasion; significant voiding symptoms, lymphovascular invasion; large or multifocal lesions; and persistent T1G3 disease at three months following BCG therapy. Advantages of early cystectomy include obtaining accurate pathologic staging, more appropriate for nerve and sexual function sparing approaches, avoiding multiple intravesical treatments thus improving a patient’s quality of life, and ultimately better cure rates.

Session Three: Translational Science in Bladder Cancer: From Bench to Bedside
Panel Co-Chairs: Gopa Iyer, M.D., Memorial Sloan-Kettering Cancer Center; John Taylor, M.D., MS, University of Connecticut Health

“Xenografting Techniques for Bladder Cancer Research” David DeGraff, Ph.D., Pennsylvania State University College of Medicine

“Translational Bladder Cancer Research with GEMMs and Chemical Carcinogenesis” Xue-Ru Wu, M.D., New York University

“Clinical Trials of Chemotherapy with Focus on Biomarkers of Response” Derek Raghavan, M.D., Ph.D., Levine Cancer Institute, Carolinas HealthCare

“ERCC2 Mutations as Predictors of Response to Cisplatin in Bladder Cancer” Eli Van Allen, M.D., Dana-Farber Cancer Institute

Translational research applies findings from basic science in the laboratory to enhance human health and well-being. It aims to "translate" findings in basic research into medical and nursing practice and meaningful health outcomes. The bench-to-bedside panel addressed how significant bladder cancer research is helping to improve patient care.

The panel began with Penn State’s David DeGraff, Ph.D. discussing xenografting techniques used in bladder cancer research. Xenografting uses a graft of tissue taken from a bladder cancer patient that is then embedded into a mouse kidney. This enables researchers to study properties and mutations of human cancer. Noting that the biologic question drives the model selection, DeGraff highlighted the advantages and disadvantages of the four common approaches of xenografting. Tissue recombination is a cost effective and flexible xenografting technique that mixes an epithelial (cells on a surface or cavity) component with a stromal or Mesenchyme (supportive or connective cell framework) components. These can identify key structural landmarks of the bladder including extracellular matrix deposition, smooth muscle, and urothelial differentiation. DeGraff provided data demonstrating how tissue recombination provides an ideal system to understand the role of stroma and carcinoma associated fibroblasts (cells that contribute to the formation of connective tissue fibers) promote bladder cancer cell division.

New York University’s Xue-Ru Wu, M.D., provided a detailed look at the history, challenges and opportunities for use of genetically engineered mouse models (GEMMs) in bladder cancer research. Using reverse genetics, GEMMS allow researchers to analyze genes of interest to understand the biologic potential of genomic, genetic and epigenetic alterations in human bladder cancer.
Derek Raghavan, M.D., Ph.D., of the Levine Cancer Institute, began his presentation noting that the density and duration of exposure to triggers/carcinogens will alter the natural history of a cancer tumor. It also influences the patient's response to treatment. In crafting models to study bladder cancer, Raghavan notes the challenge is getting the density and duration of exposure right to mimic the human setting. Using the example of glutathione (important in tissue oxidations) as a determinant of resistance to platinum-based chemotherapy, Raghavan noted that preclinical modeling of heterogeneity of gene expression, in context, can predict the need for multi-agent chemotherapy or new agents to treat cancer.

Eli Van Allen, M.D., of Dana-Farber, concluded the panel with a discussion of his use of clinical computational oncology. His research applies computer algorithms to examine mutations as predictors of response to therapies. He discussed an example of his work evaluating whether mutations in ERCC2, a DNA repair gene, lead to cisplatin chemosensitivity in bladder cancer. Dr. Van Allen uses large genomic datasets combined with clinical data, with the goal of adding precision to treatments for bladder cancer.

Session Four: Immunotherapy
Panel Co-Chairs: Piyush Agarwal, M.D., National Cancer Institute; Jason Efstathiou, M.D., DPhil, Massachusetts General Hospital; Matthew Galsky, M.D., Mount Sinai School of Medicine

“Introduction to Immunotherapy in Bladder Cancer” Jason Efstathiou, M.D., DPhil, Massachusetts General Hospital

“Clinical Results with Immune Checkpoint Blockade in Bladder Cancer” Elizabeth Plimack, M.D., MS, Fox Chase Cancer Center

“Dissecting the Mechanistic Basis of Immune Checkpoint Blockade in Patients” Lawrence Fong, M.D., University of California San Francisco

“The Impact of Radiation Therapy on Antitumor Immunity” Charles Drake M.D., Johns Hopkins Medicine

The treatment of disease with new therapies that stimulate the immune response to find and destroy bladder cancer cells is the first major advance in the treatment of advanced bladder cancer in 30 years. Starting with a brief historical overview of immunotherapy and cancer, Dr. Jason Efstathiou from Mass General noted the early association between febrile illness (having a fever with an unknown cause) and cancer regression. In 2015, progress in immunotherapy in bladder cancer has been informed by other disease sites (i.e. melanoma and renal cell carcinoma). Bladder cancer immunotherapy began with BCG (Bacille Calmette-Guerin) stimulating an adaptive immune response. He noted that ongoing studies are testing immunotherapy and radiation therapy with and without other potential therapeutic strategies.

Fox Chase Cancer Center's Betsy Plimack, M.D., suggested recent clinical results seen in immune checkpoint blockade used in bladder cancer may bring new advances in bladder cancer therapy. Starting with a neoadjuvant Ipilimumab (a monoclonal antibody that works to activate the immune system) “window of opportunity” study in urothelial cancer, Plimack highlighted the numerous advances in PD-L1 and PD-1 inhibitor immunotherapy over the last fifteen months.

From the University of California San Francisco, Larry Fong, M.D., took the discussion further while describing the mechanistic basis of immune checkpoint blockade in patients. He focused on research into T-cell clonality from studying prostate cancer and melanoma as models for bladder cancer research. Fong concluded with the suggestion that T-cell receptor sequencing allows for the characterization and tracking of T-cell immune responses and does not require knowledge of the relevant antigens.

Lastly, Charles Drake, M.D., of Johns Hopkins Medicine, addressed the impact of radiation therapy on anti-tumor immunity. He used a patient case study to showcase how radiation therapy may release molecules that activate immune cells. Radiation therapy may allow the T-cells to make it easier to recognize and kill the tumor cell. Radiation seems to change the quality and quantity of the antigens. Questions regarding radiation therapy dose and schedule and timing of immunotherapy remain unanswered.
2013 Young Investigator Award Research Reports

BCAN launched its Young Investigator Awards in 2013 to support the development of outstanding research scientists and clinical cancer research investigators who have demonstrated a commitment to improving the understanding and treatment of bladder cancer. Each award is for $100,000, over a two-year period. Three awards were granted in 2013, and those investigators presented their final reports:

- David DeGraff, Ph.D., Penn State University Hershey, “Transcriptional Control of Bladder Cancer Tumorigenesis”
- Gopa Iyer, M.D., Memorial Sloan-Kettering Cancer Center, “Identifying Predictors of Response to mTOR-targeted Therapies in Bladder Cancer”
- Debashis Sahoo, Ph.D., University of California San Diego, “High-resolution molecular analysis of CD47-mediated immune escape in bladder cancer”

John Quale Traveling Fellowship Awards

Started in 2009, the John Quale Travel Fellowship Program provides stipends to defray travel-related costs for early career investigators interested in bladder cancer research to attend the Think Tank Meeting. Four young investigators were awarded John Quale Travel Fellowships to present their research at the 2015 Think Tank Meeting:

- Abdul Banday, Ph.D., National Cancer Institute
- Max Kates, M.D., Johns Hopkins Medical Institutions
- Randy Sweis, M.D., University of Chicago
- Huyen Nguyen, Ph.D., The Ohio State University

Collaborative Small Group Discussions

Think Tank attendees participated in small group discussions during the meeting on a variety of different topics. Three working groups continued their collaborative efforts that had begun at previous Think Tank meetings: Survivorship Working Group, Upper Tract Disease Working Group and the Patient-Centered Outcomes and Policy Working Group. Nine other small groups continued the discussion of panel presentations or explored specific issues in bladder cancer treatment, including variant histology in bladder cancer; optimizing intravesical immunotherapy; optimizing surgical outcomes; mechanisms of invasion and metastasis.

Special thanks to the 2015 Think Tank Steering Committee

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- Program Chair: Ashish Kamat, M.D., MD Anderson Cancer Center
- Program co-Chair: Jonathan Rosenberg, M.D., Memorial Sloan-Kettering Cancer Center

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